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# The Role of Asymmetric Dimethylarginine in the Atherosclerotic Process of Cardiovascular Disease in Patients With Chronic Renal Disease

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Running title: Asymmetric Dimethylarginine and renal failure

**Abstract**

Introduction: Plasma asymmetric dimethylarginine (ADMA) is a potential risk factor for cardiovascular diseases. We performed a study toassess the relationship between ADMA and premature atherosclerosis as determined by carotid intima-media thickness (CIMT) and coronary artery calcification score (CACS) in uremic patients.

Methods: The study was performed on 38 predialysis and 39 dialysis patients and 46 controls. Plasma ADMA were determined. Carotid IMT was measured by ultrasonography. CACS was measured by multislice computed tomography.

Results: CIMT values were higher in dialysis (0.78±0.16 mm) and predialysis patients (0.74±0.20 mm) than control group (0.56±0.11 mm) ( $p<0.001$). CACS were found to be higher in dialysis (701.97±1437.03) and predialysis patients (64.79±143.02) than controls (28.95±158.65) ($p=0.003$. $p<0.001$ respectively). Similarly, plasma ADMA levels were higher in dialysis (1.44±0.58 µmol/L) and predialysis patients (1.04±0.43 µmol/L) than controls(0.69±0.56 µmol/L) ($p<0.001$).

In the analysis of total cohort carotid IMT showed positive correlation with age, creatinine, Ca-P product, PTH, ADMA, nitrate and CACS; and negative correlation with HDL cholesterol. CACS showed positive correlations with age, ALP, PTH, ADMA, nitrite, carotid IMT, and showed

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negative correlation with HDL cholesterol. ADMA showed positive correlations with serum creatinine, Ca-P product, ALP, PTH, TG, carotid IMT, and showed negative correlation with MDRD-GFR and HDL cholesterol levels. ADMA and CACS showed positive correlations withduration of dialysis and duration of renal failure.

Conclusions: Because of having significant correlations with calcification parameters, dyslipidemia, inflammation and malnutrition; ADMA levels can be used as as a determinant for atherosclerotic process of cardiovascular disease in chronic renal failure.

**Keywords:** Atherosclerosis, asymmetric dimethylarginine, coronary artery calcification score, carotid intima-media thickness, chronic renal failure.

## INTRODUCTION

Chronic kidney disease (CKD) is an irreversible and progressive disease characterized by the progressive nephron loss which develops due to various ethnologies, and disease itself has high mortality and morbidity rates[1]. The most important cause of increase in mortality and morbidity in CKD is cardiovascular diseases derived from rapid and early development of atherosclerosis[2].Currently, some studies reported that atherosclerosis and related vascular diseases manifest at the early stages of CKD, before reaching to end stage renal disease (ESRD)[3]. The presence of traditional atherogenic risk factors (age, increase in blood pressure, diabetes, dyslipidemia, obesity) which were demonstrated by Framingham study and other epidemiological studies have not fully clarified the increased atherogenesity in CKD and high morbidity and mortality rates due to atherogenic diseases[4,5]. There are also additional risk factors associated with uremia. These risk factors include volume load related hypertention, anaemia, calcium-phosphorous metabolic disorders, hyper catabolism, chronic inflammation and oxidative stress. In uremic patients increased pro inflammatory cytokines and oxidative stress are thought to play an important role in the development of atherosclerosis[6]. There are limited studies intending to show predisposing risk factors contributing to calcification as oxidative stress and inflammation.

Nitric oxide (NO) is a strong anti-atherogenic molecule which has vasodilating, reducing monocyte adhesion-thrombolytic aggregation and inhibiting smooth muscle proliferating properties is synthesized by nitric oxide synthease (NOS). Asymmetric dimethlyarginine (ADMA) is an endogenous inhibitor of NOS. After demonstrating the increase in ADMA levels in a study conducted with patients undergoing dialysis in 1992, influence of ADMA in the development of atherosclerosis in ESRD was investigated in limited number of studies. In 1999it was reported that ADMA levels had increased significantly in dialysis patients with atherosclerotic disease compared to dialysis patients without atherosclerotic disease[7]. In 2002 increased ADMA levels was reported to be strong and independent predictor of increase in carotid artery intimae media thickness (IMT) in dialysis patients[8]. Increased carotid IMT is an indicator of sub clinic atherosclerotic disease. Carotid IMT measurement is commonly used in the early diagnoses of asymptomatic atherosclerotic disease[9]. These studies suggested that ADMA might have key role on atherosclerosis and atherosclerosis dependent morbidity and

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mortality in CKD patients[7, 8]. Most of studies related to factors which contribute increases atherosclerotic diseases were conducted in haemodialysis (HD) patients[10]and studies performed with patients in early stages of disease are in limited number[11].

Coronary artery calcification score isa non-invasive method which has high sensitivity and predictive value in discovering atherosclerosis in CKD patients[12].Recently performed small number of studies identified that there was a positive correlation between coronary artery calcification score and ADMA levels. On this subject, no studies were performed including both patients with chronic kidney disease and patients undergoing renal replacement therapy.

Therefore we investigated the relationship between ADMA and carotid IMT and coronary artery calcification score (CACS) which are predictor of coronary artery disease, in control group and in predialysis patients who have yet not reached to end stage of kidney disease and chronic haemodialysis patients.

## MATERIALS AND METHODS

Total of 77 patients of which 39 patients undergoing dialysis program and 38 predialysis patients as well as 46 healthy control patients were enrolled in the study. Haemodialysis patients were undergoing 3 dialysis sessions per weekly, each session was lasted 4 hours. Predialysis patients were selected from patients whose follow up performed in nephrology clinic. Control group consist of individuals who have no history of cardiac disease and kidney failure as well as matched individuals in terms of age, gender.
All patients enrolled in the study were questioned for hypertension, hyperlipidemia, chronic obstructive pulmonary disease, coronary artery disease, periferic artery disease, cardiac and cerebrovascular diseases and their symptoms. Patients with documented atherosclerotic cardiac artery disease, periferic artery disease and intended symptoms were not included in the study. Those individuals with suspected acute renal failure, exposure to contrast agent (in the past one month), diabetics, malignancy, infectious symptoms and hemodynamic ally unstable conditions were not included in the study. The ethical approval was taken from the institution.

### Laboratory analysis

All patients' blood and urine samples were collected at 8 am after 12 hours of fasting. In dialysis patients blood samples were collected at midweek before the second dialysis session. ADMA, nitrate, nitrite, homocystein, Hs-CRP, Lipoprotein (a) blood samples were taken into anti-coagulant free tubes and turned at a speed of 4000 rev/minutes for 7 minutes, after serum were separated, whole blood samples were stored at – 80 $^0$C. After all samples collected nitrate, nitrite levels were analysed by enzymatic methods, wheras others by ELISA method.

### Carotid intimae-media thickness measurement

Carotid IMT measurement of all individuals participating in the study was performed by the same radiologist. For all patients, one at the main carotid artery (2 cm proximal to bulb), one at

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the bulb level and one at the level of each of internal carotid artery, 3 bilaterally measurements were performed. As a whole total 18 measurements were performed for each patients, and mean values were calculated and IMT values were determined for that patient. No measurement was performed locations where a thermo plaque was seen.

### Measurement of coronary artery calcification score

Measurement of coronary artery calcification score was performed by using multi-slice BT (Philips Brilliance 16 slice CT, Holland) device, contrast agent was not used during this procedure. All investigations were performed by using parameters of 3 mm slice thickness and 2.4 mm table movement, 55 mA, 120 kV, gantri rotation time of 0.5 seconds and calcium scoring agoritm. The amount of calcium in the coronary arteries was performed with the help of " Accu Image Workstation " and by using Agatston scoring. By adding calcium score in all coronary arteries total Agatston score was found.

### Statistical analysis

"SPSS for Windows version 17 Statistics" was used for data input and statistical analysis. Frequencies for categorized data type (qualitative) variations and standard deviation for continuous data type (quantitative) variation was calculated as usual after data corrections completed, from pair wise comparisons P values were calculated; in the case of categorized data type variations were present, chi-square test, if one of variable was continuous variable and distribution was appropriate t-test or one -way Anova parametric tests, if distribution was inappropriate non-parametric tests were used. If both variables have continuous data, again considering distribution of variable, parametric (Pearson r) or non-parametric (Spearmen p) correlation tests were used. Statistical significance was determined as $p < 0.05$.

## RESULTS

Our study included 39 patients in chronic haemodialysis patients with mean age of 48.35 ±11.66 years, 38 predialysis patients with chronic kidney disease with mean age of 49.76 ±13.49 years and 46 individuals of control group with mean age of 49.54 ± 11.51 years. All groups were found similar in terms of age, gender and blood pressure values ($p < 0.05$). In predialysis group hypertension frequency (% 68.4) was found higher than control group (32.5 %)and dialysis group (53.8 %).Demographic characteristics of groups were given in Table 1.

Since diabetes was an exclusion criteria in both predialysis and dialysis patients, hypertension took the first place at the ethnology of renal failure. Glomerulonephritis rate was 18.4 % and 15.4 % in predialysis and dialysis patients respectively. Rate of renal calculi/obstruction and polycystic kidney disease was found 10.3 % in dialysis patients and it was higher than that of predialysis group.

Haemoglobin and albumin levels were found significantly lower in dialysis and predialysis groups compared to control. Uric acid, fibrinogen, ferritin and CRP levels were found

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significantly higher in both predialysis and dialysis groups compared to control. Comparative laboratory findings of all groups were shown in Table 2.
Markers of inflammation and atherosclerotic parameters and carotid IMT and CACS values of all groups were shown in Table 3. ADMA values were significantly higher in dialysis group than predialysis and control group. Carotid IMT values were similar in predialysis and dialysis groups. These values were significantly higher than control group. CACS was significantly higher in dialysis group than predialysis and control group ($p= 0.008$ and $p < 0.001$ respectively). It was also higher in predialysis group than control group ($p= 0.003$).

## CORELATION ANALYSIS OF CAROTID IMT, CACS AND ADMA VALUES BETWEEN GROUPS

Since control group also had traditional risk factors in terms of atherosclerotic disease, all groups were evaluated together and when distribution was expanded positive correlation was detected between carotid IMT and age, cigarette exposure time, uric acid, ADMA and CACS (Table 4). In addition, negative correlation was detected between ADMA and HDL cholesterol, MDRD-GFR. We found a positive correlation between ADMA and fibrinogen, CaxP product, PTH, ALP, ferritin and carotid IMT which somehow supports inflammation and atherosclerotic relationship.

In total kohort in the logistic regression analysis, CACS remained significantly associated with PTH ($\beta$=0.386, P=0.000) In binary logistic regression analysis the patients CACS>600remained associated with cigarette (Multivariate OR 4.25, 95% CI: 1.18-15.34) and age (Multivariate OR 1.08, %95 CI: 1.02-1.15) We also found that elevation of the ADMA level was significantly associated with MDRD-GFR ($\beta$= -0.007,95% CI for $\beta$: -0.009-(-0.005)). Also in the lineer regression model CIMT remained significantly associated with age ($\beta$=0.239, P=0.003), cigarette ($\beta$=0.237, p=0.004), nitrate ($\beta$=-0.162, p=0.046) and PTH ($\beta$=0.175, p=0.039).
In total kohort and in all CKD patients there was a positive correlation between Lp (a) and insulin level and HOMA index.

When groups were investigated one by one, in dialysis group; negative correlation was detected between carotid IMT and waist circumference (p=0.028), albumin (p= 0.047) and uric acid (p= 0.017). Positive significant correlation was detected between carotid IMT and PTH (p= 0.026) and CACS ($p < 0.001$) which are strong indicators of atherosclerosis. In dialysis group positive correlation was shown between CACS and duration of RRT (p= 0.017), PTH (p= 0.44), ALP ($p < 0.001$) and carotid IMT ($p < 0.001$). Positive significant correlation was found between ADMA and duration of RRT (p= 0.017) and Hs-CRP (p=0.046).

In predialysis group; positive significant correlation was detected between carotid IMT and age (p= 0.030), ALP (p=0.043), creatinine (p=0.038) and CACS (p=0.035). Positive and very close to significant correlation was detected between carotid IMT and duration of CKD (p= 0.057). Negative correlation was detected between HDL and carotid IMT (p=0.018). Positive correlation was detected between CACS and age ($p< 0.001$), creatinine (p=0.0013), carotid IMT (p= 0.003) in predialysis group. Negative correlation was detected between albumin and CACS (p=0.011).

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In all CKD patients; statistically significant positive correlation was detected between CACS and duration of CKD (p=0.042), PTH (p=0.001), ALP (p<0.001), ferritin p=0.002) and carotid IMT (p<0.001) , negative correlation was detected between creatinine clearence (p=0.024) and HDL cholesterol (p=0.006). In logistic regression model CACS significantly associated with PTH ($\beta$=0.223, P=0.046) and carotid IMT ($\beta$=0,410, P<0.0001). Similarly it was detected that ADMA values exhibited positive correlation with duration of CKD (p=0.002) and creatinine (p=0.049).

In control group; positive correlation was shown between carotid IMT and age (p <0.001), Hs-CRP (p=0.020) and CACS (p=0.0021). Positive correlation was detected between CACS and age (p< 0.001), waist circumference (p= 0.014), cigarette exposure time (p= 0.001), body weight (p <0.001), hemoglobin (p=0.028), and inflammatory and atherosclerotic markers Hs-CRP (p=0.013), homocysteine (p=0.015) and carotid IMT (p <0.001).

## DISCUSSION

In this study we found that CACS and CIMT were significantly increased in non-diabetic predialytic patients (Stage 3-4-5) and hemodialytic patients without documented atherosclerotic disease. The findings of increased CACS and CIMT in chronic renal failure patients comparison to a control group with similar age and gender distribution can be considered as an indicator of accelerated atherosclerosis. Even in predialysis patients with mean GFR values of 35 ml/min/1.73 $m^2$ CACS and carotid IMT values were found significantly higher than control group indicated that development of atherosclerosis started from the early stages of kidney disease. In addition, a positive significant correlation was detected between carotid IMT and CACS in all groups. Since we aimed to investigate the cardiovascular influence of uraemia itself, control group specifically chosen from individuals without renal dysfunction but having traditionally atherosclerotic risk factors. The detection of positive correlation between ADMA and creatinine in control group individuals whose creatinine levels were even in the normal range anda positive relationship between ADMA and duration of CKD in predialysis patients and RRT in haemodialysis patients were important findings.

Kiel stein et al investigated the relationship between asymmetric dimethyl arginine and increased atherosclerosis development in dialysis patients and reported that dialysis patients with prominent atherosclerotic disease had higher ADMA levels than non-atherosclerotic patients[10]. Zoccali et al[13]reported that in patients undergoing dialysis treatment, ADMA level was 3 fold higher than healthy individuals and hemodialysis patients with asymmetric dimethyl argentine level above of 75 %,risk of cardiovascular events and mortality rates were significantly higher. It was also shown that an increase in ADMA level per 1 μmol/L led 26 % increases in mortality resulting from various reasons. In our study we also observed that ADMA levels in dialysis and predialysis group were significantly higher than control group. Zocali et al also subsequently showed that asymmetric dimethyl arginine was found to be the most important and independent risk factor of carotid IMT after patient agein haemodialysis patient group of 225 subjects[13]. The presence of stronge and independent relationship between ADMA and carotid IMT in healthy individuals was also shown in patients undergoing dialysis[14]. Nanayakkara et al[12]showed that increased ADMA levels, patient age and mean arterial pressure were predictors of increased carotid IMT in non-diabetic patients with GFR level in the range of 15-70 ml/min/1.73 $m^2$. In

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our study, we observed that age, CACS and HDL cholesterol were determinant factors for carotid IMT development in all CKD patients. In total cohort, positive correlation was detected between carotid IMT and ADMA. High ADMA levels serve as a predictor for intima media thickness and coronary artery events[15, 16]. Zoccoli et al noticed that ADMA levels have significant relationship withcarotid IMT and in regression analysis they were also observed that ADMA and CRP interaction was an independent marker in the progression of intimal lesion[17]. Similar to our study, Kobayashi et al in their first study indicating the relationship between ADMA, insulin resistance and CACS, showed that ADMA levels were negatively correlated with GFR and positively correlated with CACS in CKD patients[18]. These at hours detected that patients with CACS > 600 have higher serum ADMA level, fibrinogen, serum creatinine, P, CaxP and lower creatinine clearence in 24-hour urine compared to patients with CACS< 50. In fact similar results were obtained in our study, in addition detection of positive correlation between ADMA levels and carotid IMT, support that ADMA is an independent risk factor for atherosclerosis and a determinant for vascular calcification. Iribarren et al compared young adults with coronary artery calcification but with normal kidney function to control group, and they determined significant independent relationship between ADMA and CACS degrees in linear regression in CARDIA study[19]. Because of this in our study when all groups were evaluated all together, detection of significant correlation between ADMA and CACS appears to be impressive.

In total cohort detection of significant positive correlation between ADMA and serum TG level, serum P level, CaxP product, PTH, ALP, carotid IMT and coronary artery calcification score as well as rapid increase in ADMA levels following decline of GFR, indicate the importance of ADMA in development of accelerated atherosclerotic vascular process. It was demonstrated that traditional/non traditional risk factors such as increased blood pressure, dyslipidemia, anemia, oxidative stres, inflammation as an inducer of atherosclerosis process led to endothelium dysfunction by decreasing NO bioavailability[20].Therefore, it has been proposed that ADMA might bea bridge for the other risk factors by inbiting nitrite oxide and causing endothelium dysfunction at the first step of atherosclerotic development and will also start atherosclerotic process[21].We detected that CACS values were higher in dialysis patient than predialysis and control group, and CACS values were higher in predialysis group than control group. Age was correlated with CACS in control, predialysis, and all CKD patients. It was observed that coronary artery calcium score was positively related with age. We detected a positive correlation between CACS and duration of dialysis in dialysis patient and duration of CKD in all CKD patients. Age and duration of dialysis were recognized as independent, irreversible, important risk factors for calcification and cardiovascular events and this fact was demonstrated in numerous studies[22,23]. Vascular calcification is not a problem for only elderly, it is also problem for young dialysis patients (age range 20-30 years). Goodmann et al

Demonstrated that in young end stage renal disease (ESRD) patient's coronary artery calcification occurs much earlier than normal population[23]. In this group of patient increase in vascular calcification showed positive correlation with P level CaxP and daily calcium intake[23]. Similar findings were also observed by Eifinger[24] and Oh[25]. In our study, positive correlation was detected in CACS and PTH, ALP. Mortality rates increase in patients with high PTH levels.

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It is important to control hyperphosphatemia and hyperparathyroidism adequately for decreasing themortality[26]. Goodman at.al. Found that CaxP values were significantly higher in ESRD patients with artery calcification than patients without artery calcification[23]. We also detected positive significant correlation between carotid IMT and P, CaxP value, PTH, ALP in total cohort. Hyperphosphatemia, hypocalcaemia, hyperparathyroidism induce vascular calcification by impairing function of inhibitory molecules[27]. Hyperparathyroidism causes atherosclerosis and myocard hypertrophy by increasing intracellular calcium in myocard cells[28].

We detected significant negative correlation between carotid IMT and lipid parameter of HDL cholesterol. The most common lipid abnormalities were increase in serum TG levels and decrease in HDL cholesterol levels in ESRD patients. Inflammation and malnutrition may cause to decrease cholesterol levels. In our study, the lower total cholestrol and LDL cholesterol levels and albumin levels and higher inflammatory markers such as CRP, fibrinogen in predialysis and dialysis group compared to control group support this effect of inflammation and malnutrition. In CKD patients with inflammation and malnutrition, correlation was observed between lowserum cholesterol levels and cardiovascular mortality[29]. According to clinical results, when compared to cardiovascular risk factors in normal population, there is a reverse correlation in cronic kidney disease patients. This reverse correlation is known as reverse epidemiology[30]. When all study group was investigated negative correlation between carotid IMT and total cholesterol, LDL cholesterol, albumin, waist circumference and BMI and positive correlation with ferritin and fibrinogen were detected. Similarly, Savage et al showed correlation between serum albumine level and carotid IMT and carotid plaques in 24 CKD patients[31]. In some studies increase in calcium score and rapid progression was correlated with dyslipidemia[32,33]. We detected positive correlation between coronary artery calcium score and triglyceride, and negative correlation with HDL cholesterol in all CKD patients. This correlation supports the point of view that coronary arterial calcification is an indicator of atherosclerosis.

In our study among the uremia associated risk factors other than traditional risk factors such as ferritin and nitrate levels correlated positively with carotid IMT. It was known that high levels of serum ferritin is an indicator of poor prognosis and also responsible for the hospitalization and early deaths in haemodialysis patients[34].

There are limited number of studies available intending to study the relation of calcification with oxidative stres and inflammation[35]. In studies conducted in dialysis patients regarding coronary arterial calcification, a positive correlation was shown between serum CRP levels and other inflammation markers[36]. We detected significant positive correlation between CACS and fibrinogen, Lp (a), ferritin, but negative correlation with albumin in total kohort. When all CKD patients evaluated positive correlation was observed between CACS and TG, ferritin and serum creatinine, negative correlation was observed between CACS and MDRD-GFR and HDL cholesterol. All these findings support the fact that as duration and severity of CKD increase, CACS and atherosclerosis also increase. In all groups a significant positive correlation between carotid IMT and CACS which is one of the best indicators of atherosclerosis is also noteworthy.

In present study we detected that HOMA index was significantly higher in dialysis group than predialysis and control group. In total kohort and in all CKD patients there was a positive

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correlation between Lp (a) and insulin level and HOMA index. It is known that insulin resistance starts when GFR is below 50 ml/sec in non-diabetic uremic patients[37].

As a conclusion, this study shows that compared to general chronic kidney disease population, even in young, non- diabetic, stage 3-4 CKD patients have widespread atherosclerosis, reveal that atherosclerosis started in the early stages of chronic kidney failure and process continues rapidly with renal replacement therapies. Moreover, ADMA may have an important rolein the process of atherosclerotic disease and coronary artery calcification in uremic patients and might bea new and meaningful biomarker of cardiovascular complications in CKD. However future studies are needed to establish the use of ADMA in daily clinical practice.

Declaration of interest: The authors report no conflicts of interest.

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Tablo 1.Demographic characteristics of groups

| | Control<br>Mean ±SD or % (n)<br>(N:46) | Predialysis<br>(N:38) | Dialysis<br>(N:39) | P value |
|---|---|---|---|---|
| Age (year) | 49.54±11.51 | 49.76±13.49 | 48.35±11.66 | 0.846 |
| Sex (F/M) | 26/20 | 18/20 | 13/26 | 0.101 |
| Hypertension | 32.5 | 68.4 | 53.8 | **0.004** |
| Hyperlipidemia | 52.2 | 50 | 56.4 | 0.848 |
| Cigarette | 30.4 | 52.6 | 53.8 | **0.048** |
| SBP (mmHg) | 120±13.4 | 124±18.5 | 122±12.0 | 0.700 |
| DBP (mmHg) | 77±8.8 | 78±11.5 | 75±7.8 | 0.377 |
| MAP (mmHg) | 91±9.5 | 94±12.6 | 90±8.2 | 0.571 |
| Pulse pressure (mmHg) | 43±9.6 | 45±13.7 | 46±9.8 | 0.306 |
| Weight (kg) | 74.1±9.1 | 66.5±13 | 68.5±12.8 | **0.024** |
| Height (m) | 1.61±0.82 | 1.64±0.97 | 1.66±0.92 | 0.063 |
| waist circumference | 97.9±8.5 | 90.6±12.2 | 90.9±11.5 | **0.002** |
| BMI ($kg/m^2$) | 28.7±4.3 | 24.5±3.6 | 24.9±4.3 | **<0.001** |

(SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean artery pressure, BMI: Body mass index)

Tablo 2.Comparative laboratory finding of all groups

| | Control[c]Mean ±SD or % (n) | Predialysis [p] | Dialysis[d] | P value | P values (Subgroup analysis) |
|---|---|---|---|---|---|
| WBC (K/µL) | 7528±1965 | 7625±2129 | 7908±1965 | 0.671 | c=p=d |
| Hb (gr/dl) | 13.46±1.74 | 11.68±1.58 | 11.38±1.63 | **<0.001** | **c>p=d** |
| Creatinine (mg/dl) | 0.83±0.14 | 2.68±1.1 | 7.21±2.46 | **<0.001** | **c<p<d** |
| Albumin (g/dl) | 4.56±0.22 | 4.08±0.59 | 4.25±0.49 | **<0.001** | **c>p=d** |
| Uric ascite (mg/dl) | 4.69±1.5 | 6.82±1.58 | 5.76±1.62 | **<0.001** | **c<p<d** |
| Fibrinogen | 435.86±147 | 594.73±173.6 | 615.89±143 | **<0.001** | **c<p=d** |
| CRP (mg/dl) | 0.54±0.54 | 0.80±0.63 | 0.90±0.67 | **0.007** | c<d=p |
| Insulin (µIU/ml) | 7.84±3.74 | 9.34±6.56 | 14.84±13.82 | **0.025** | c=p<d |
| Total cholesterol (mg/dl) | 197.58±36.39 | 178.44±40.55 | 179.48±55.19 | **0.034** | **c>p=d** |
| LDL (mg/dl) | 123.80±32.78 | 105.86±29.18 | 104.69±42.07 | **0.020** | **c>p>d** |
| TG (mg/dl) | 143.83±70.16 | 154.65±79.79 | 196.43±92.76 | **0.01** | c<d=p |
| HDL (mg/dl) | 46.17±10.21 | 42.02±17.59 | 36±13.37 | **<0.001** | **c>p=d** |
| Calcium (mg/dl) | 9.1±0.4 | 8.9±0.6 | 9.0±0.8 | 0.672 | c=p=d |
| Phosphor (mg/dl) | 3.4±0.6 | 4.1±0.8 | 4.9±0.9 | **<0.001** | **c<p<d** |
| Ca-P product (mg/dl) | 30.97±5.94 | 36.57±6.81 | 44.33±10.56 | **<0.001** | **c<p<d** |

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| | | | | | |
|---|---|---|---|---|---|
| MDRD-GFR (ml/dk) | 108.41±21.28 | 32.04±12.42 | 10.32±5.61 | **<0.001** | **c>p>d** |
| PTH (pg/ml) | 58.86±21.74 | 199.88±174.95 | 536.23±648.6 | **<0.001** | **c<p<d** |
| ALP (IU/L) | 63.13±19.48 | 72±25.8 | 139.1±138.27 | **<0.001** | c=p<d |
| Ferritin (ng/dl) | 58±45.98 | 148.09±137.31 | 540.83±531.32 | **<0.001** | **c<p<d** |
| Proteinuria (mg/gün) | 140.58±196.08 | 1809.29±2901.9 | 1608.46±1508.8 | **<0.001** | **c<p=d** |
| HOMA-IR | 1.90±0.91 | 2.19±1.62 | 3.25±3.13 | **0.01** | c<d=p |

(WBC: White blood count, Hb: haemoglobin, CRP:C-reactive protein, MDRD-GFR: Modification of diet in renal Deseases Glomeruler filtration rate, PTH: parathormone, ALP: Alkaline phosphatise, HOMA-IR: HOMA insulin resistance)

Tablo-3.Marker of inflammation and atherosclerotic parameters and carotid IMT and CACS values of all groups

| | Control<br><br>Mean ±SD or % (n) | Predialysis | Dialysis | P value | P value (subgroups analysis) |
|---|---|---|---|---|---|
| Hs-CRP | 3.51±3.28 | 4.41±4.04 | 4.43±4.33 | 0.455 | c=p=d |
| ADMA | 0.69±0.56 | 1.04±0.43 | 1.44±0.58 | **<0.001** | **c<p<d** |
| Homosisteine | 13.74±6.42 | 14.0±6.09 | 14.46±7.25 | 0.882 | c=p=d |
| Lipoprotein (a) | 23.77±14.01 | 35.63±24.48 | 40.07±24.42 | **0.002** | **c<p=d** |
| nitrite | 30.95±18.14 | 27.48±35.90 | 38.53±29.63 | **0.004** | **c=d>p** |
| nitrate | 108.54±59.78 | 45.25±44.58 | 94.22±51.05 | **<0.001** | **c=d>p** |
| Total nitrite | 139.49±64.67 | 72.74±11.7 | 132.76±66.81 | **<0.001** | **c=d>p** |

| | | | | | |
|---|---|---|---|---|---|
| | | 5 | | | |
| CIMT | 0.56±0.11 | 0.74±0.20 | 0.78±0.16 | **<0.001** | **c<p=d** |
| CACS | 28.95±158.65 | 64.79±143.02 | 701.97±1437.03 | **<0.001** | **c<p<d** |

(Hs-CRP: High sensitive C reactive protein)

Tablo-4. The correlation of demographic and laboratory parameters with CIMT, CACS and ADMA

| | CIMT | | CACS | | ADMA | |
|---|---|---|---|---|---|---|
| | rvalue | pvalue | rvalue | p value | rvalue | pvalue |
| Age | 0.246 | **0.006** | 0.362 | **<0.001** | 0.144 | 0.112 |
| waist circumference | -0.225 | **0.012** | -0.101 | 0.265 | -0.062 | 0.495 |
| cigarette | 0.236 | **0.009** | 0.341 | **<0.001** | -0.008 | 0.932 |
| SBP | 0.071 | 0.437 | 0.111 | 0.220 | 0.097 | 0288 |
| DBP | -0.140 | 0.121 | -0.021 | 0.815 | 0.155 | 0.087 |
| BMI | -0.246 | **0.006** | -0.180 | 0.046 | -0.238 | **0.008** |
| Hb | -0.276 | **0.002** | -0.164 | 0.069 | -0.194 | **0.031** |
| Creatinine | 0.318 | **<0.001** | 0.429 | **<0.001** | 0.411 | **<0.001** |
| Albumin | -0.272 | **0.002** | -0.298 | **0.001** | -0.077 | 0.397 |
| Uric ascite | 0.180 | **0.046** | 0.093 | 0.304 | 0.037 | 0.688 |
| Fibrinogen | 0.278 | **0.002** | 0.238 | **0.008** | 0.273 | **0.002** |
| CRP | 0.173 | 0.056 | 0.137 | 0.130 | 0.059 | 0.518 |
| T cholesterol | -0.218 | **0.016** | -0.224 | **0.013** | 0.026 | 0.776 |
| LDL | -0.182 | **0.043** | -0.206 | **0.022** | 0.073 | 0.423 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| TG | 0.040 | 0.660 | 0.199 | **0.028** | 0.177 | 0.050 |
| HDL | -0.276 | **0.002** | -0.371 | <**0.001** | -0.221 | **0.014** |
| Ca | 0.021 | 0.818 | 0.032 | 0.725 | -0.033 | 0.716 |
| P | 0.185 | **0.040** | 0.112 | 0.218 | 0.238 | **0.008** |
| Ca-P product | 0.191 | **0.034** | 0.144 | 0.111 | 0.212 | **0.019** |
| MDRD-GFR | -0.488 | <**0.001** | -0.454 | <**0.001** | -0.504 | <**0.001** |
| PTH | 0.328 | <**0.001** | 0.235 | **0.009** | 0.376 | **0.001** |
| ALP | 0.254 | **0.005** | 0.239 | **0.008** | 0.307 | **0.001** |
| Ferritine | 0.252 | **0.005** | 0.477 | <**0.001** | 0.247 | **0.006** |
| Proteinuria | 0.098 | 0.365 | 0.134 | 0.213 | 0.018 | 0.869 |
| HOMA-IR | 0.115 | 0.205 | 0.017 | 0.853 | 0.065 | 0.475 |
| Hs-CRP | 0.068 | 0.456 | 0.160 | 0.078 | 0.153 | 0.091 |
| ADMA | 0.209 | **0.020** | 0.241 | **0.007** | - | - |
| Homosisteine | 0.059 | 0.517 | 0.108 | 0.233 | 0.044 | 0.629 |
| Lp (a) | 0.148 | 0.106 | 0.271 | **0.003** | 0.148 | 0.106 |
| Nitrite | 0.062 | 0.493 | 0.175 | 0.053 | 0.047 | 0.605 |
| Nitrate | -0.227 | **0.012** | -0.110 | 0.224 | -0.052 | 0.570 |
| CACS | 0.450 | <**0.001** | - | - | 0.144 | 0.111 |
| CIMT | - | - | 0.604 | <**0.001** | r=0.209 | **0.020** |